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REMARKS

Claims 23, 24, 26 and 28-37 have been examined. By this submission, claims 23, 24, 29 and 31 have been amended. Claims 23 and 37 have been amended to correct a grammatical error referring to the prostate antigen and the recipient, respectively. Claims 24 and 29 have been amended to recite a particular embodiment of the invention disclosed in the specification as filed at, for example, page 5, line 10 and page 13, lines 26 and 27. Claim 31 has been amended to conform the language of the claim for consistency with claim 23 upon which it depends. No new matter has been added by the present amendments. Applicants respectfully request reconsideration of the claims currently pending in the application in light of the amendments above, the below remarks, and in view of the amendments and remarks set forth in Applicants' Response After Final Rejection.

Applicant's representative wishes to thank the Examiner for the courtesy of allowing the January 10, 2003 interview to discuss the Response after Final Rejection filed December 5, 2002. During that interview the pending rejections under 35 U.S.C. §112 and §102 were discussed. The Examiner indicated at that time that the amendments to claim 23 submitted in the Response After Final Rejection would overcome the rejection under 35 U.S.C. § 112, second paragraph, if specific pages of the description supporting the amendments were set forth. Further, the Examiner noted that similar amendments might be made to dependent claim 31 for consistency. These rejections were maintained by the Examiner in the Advisory Action. No agreement was reached during the interview in regard to the rejection under 35 U.S.C. § 102. Additional remarks relating to each of the specific rejections are set forth below.

Rejections Under 35 U.S.C. § 112:

Claims 23, 24, 26 and 28-37 remain rejected under 35 U.S.C. § 112, second paragraph, the Examiner believing that the phrase "directly isolated" is confusing.

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Amendments to claim 23 were presented in the Response After Final Rejection dated December 5, 2002. During the January 10, 2003 interview the Examiner indicated that the amendments presented could overcome the rejection if support in the specification was set forth with particularity. An Advisory Action dated March 25, 2003 has now been received wherein the Examiner has indicated that the phrase "having the same number of cells that has not been exposed *in vitro* to the prostate antigen" has not been taught by the specification.

Applicants believe the phrase "having the same number of cells that has not been exposed *in vitro* to the prostate antigen" is taught by the specification and respectfully direct the Examiner to, for example, page 10, lines 8-12 and Section 6 beginning at page 19, line 21 of the specification as filed. Compositions comprising isolated populations of human dendritic cells that have been exposed *in vitro* to a soluble antigen are taught to have about 20 to 50 fold higher numbers of dendritic cells competent and able to activate prostate antigen specific T cells as compared to those cells not contacted with the prostate antigen. Further, in a particular embodiment provided in Section 6.4 of the specification the ability of dendritic cells to process and present prostate antigen, and further to stimulate autologous T cells of a prostate cancer patient is described. The results of these experiments are depicted in Figure 3 wherein 2 of the 4 patients demonstrated significant increases in T cell proliferation when both dendritic cells and tumor cell lysate were included in the T cell cultures. Neither tumor cell lysate alone or the same number of isolated dendritic cells alone were sufficient to process and present antigen to the T cells as evidenced by the lack of induction of T cell proliferation by these compositions. These data demonstrate and establish that a cell population having DCs isolated from peripheral blood and exposed to prostate antigen *in vitro* process and present antigen to T cells and induce proliferation. Whereas, the same number of cells not exposed to prostate antigen *in vitro* either were unable to process and present antigen to T cells as evidenced by reduced T cell proliferation, or the reduction in

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T cell proliferation resulted from fewer dendritic cells being present in the cell population competent and active to present antigen.

Further, in Section 7.1, beginning at page 27, dendritic cells were isolated from PBMCs and grown in the presence of GM-CSF and IL-4 for 7 days prior to being cryopreserved. The cryopreserved DCs were stored for a period of time, thawed, and resuspended in medium. Previously frozen T cells isolated from PBMCs obtained from the same cancer patient as the dendritic cells, were either combined with the same number of DCs alone or in combination with purified PSMA. Subsequent to six days of co-culture  $^3$ H-thymidine was added for 18 hrs to measure the rate of T cell proliferation. Figure 6 demonstrates that a highly significant increase in thymidine incorporation was observed when both previously frozen DCs and prostate antigen were included in the T cell cultures which substantiates the processing and presentation of prostate antigen by the DCs. The effect was significantly greater than that observed with antigen alone or with the same number of DCs alone but no exogenous prostate antigen.

Applicants believe that the specification teaches a control "having the same number of cells that has not been exposed *in vitro* to the prostate antigen" as set forth above. Therefore, the Examiner is respectfully requested to reconsider and withdraw the rejection of claims 23, 24, 26 and 28-37 under 35 U.S.C. 112, second paragraph.

Rejections Under 35 U.S.C. § 102:

Claims 23, 24, and 31-36 remain rejected under 35 U.S.C. § 102, the Examiner believing the claims to be obvious over Cohen *et al.* as evidenced by Sallusto *et al.*, Koch(?, [Koski]) *et al.*, and Czerniecki *et al.* for reasons the of record. In addition, during the January 10, 2003 interview with Applicants' representative and in the Advisory Action the Examiner has now set forth additional reasoning that "Koski *et al.* is cited to show the inherent property of the monocytes treated with calcium ionophore." In

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particular, the Examiner now states that the "monocytes treated with calcium ionophore taught by Cohen *et al.* would inherently have immature dendritic cells, up to 4 hrs, and even up to at least 20 hours after calcium ionophore treatment, as evidenced by Koski *et al.* who teach that monocytes CD83 expression (property of mature dendritic cells) appear within 4 hrs and peaked at 20 hours of calcium ionophore treatment." Applicants must again disagree with the Examiner.

A reference inherently discloses a claim limitation "if the prior art necessarily functions in accordance with, or includes," the claim limitation. *Atlas Powder Co. v. IRECO inc.*, 51 USPQ2d 1943, 1946 (Fed. Cir. 1999). Inherency may not be established by the probability or possibility that a claim element may result from a given set of circumstances. *Continental Can Co. USA Inc. v. Monsanto Co.*, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991). Further, while later published extrinsic evidence may be used when a cited reference is silent about an asserted inherent characteristic, that evidence must show a "universal fact or a rule of nature." *EMI Group North America Inc. v. Cypress Semiconductor Corp.*, 60 USPQ2d 1223, 1429 (Fed. Cir. 2001); MPEP § 2131.01(III), citing § 2124. "Such facts include the characteristics and properties of a material or a scientific truism." Generally, extrinsic evidence, such as a later published paper, when used to fill a gap where the asserted reference is silent about the characteristic or property, is judged according to whether one of skill in the art would recognize the presence of the limitation at issue in the reference. The skilled artisan standard applied in the analysis under anticipation is generally that as of the effective filing date of the application. An exception is only made where an unpatentable theoretical mechanism or rule of nature is recited in the claim under examination. *EMI Group North America Inc. v. Cypress Semiconductor Corp.*, 60 USPQ2d 1423, 1429 (Fed. Cir. 2001).

Cohen as previously argued by Applicants teaches a method comprising treating monocytes with a calcium ionophore for the "conversion of the large monocyte population to an activated DC-like phenotype so that they also can participate in effective

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antigen processing and presentation." Cohen, column 10, lines 30-32. It is further taught by Cohen *et al.* that it is the cells converted to an "activated DC-like phenotype" that are contacted with an antigen and predicted to process and present antigen. Applicants have previously provided extrinsic evidence that these "activated DC-like phenotype" cells can not process and present antigen. Koski *et al.* and Zhou *et al.* were cited by Applicants to provide evidence that the cells of Cohen were phenotypically the same as mature activated dendritic cells and therefore would not and could not process and present antigen. The Examiner subsequently cited Koski *et al.*, as reviewed above, for allegedly teaching that monocyte CD83 expression (a property of mature dendritic cells) appears within 4 hours and peaked at 20 hours of calcium ionophore treatment and that immature dendritic cells would be present in the cell population during the conversion process.

Applicants do not believe that immature dendritic cells in addition to those isolated from the donor must inherently be present in the conversion process described by Cohen or that Koski *et al.* unambiguously discloses their production during the process. The Examiner is respectfully directed to page 1360, left column, lines 13-16, of Koski *et al.* wherein the authors compare and contrast certain characteristics of cytokine treatment and calcium ionophore (CI) treatment stating "[t]hese contrasting kinetics do not preclude the possibility that cytokine treatment and CI treatment induce DC differentiation and/or activation through ultimately convergent molecular mechanisms." Therefore, the later published Koski *et al.* reference does not disclose either a "universal fact" or a "rule of nature" so as to be available to the Examiner to fill any gap in Cohen *et al.* Nor does Koski *et al.* even suggest the probability or possibility that monocytes treated with calcium ionophore could process antigen during the conversion of the cells to the "activated dendritic cell-like" phenotype as set forth by Cohen *et al.*. Applicants assert that the statement by Koski *et al.* demonstrates that the authors did not know or understand the mechanism by which monocytes are converted to the "activated dendritic-like phenotype" and therefore the reference can not be used as extrinsic evidence that immature dendritic cells are present as an inherent property of calcium ionophore

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treatment of monocytes. Koski *et al* merely speculate that the conversion of monocytes might possibly follows some unknown convergent pathway that results in an "activated dendritic-like phenotype" as taught by Cohen *et al*. Applicants respectfully remind the Examiner that the appearance of CD83 on the surface of the dendritic cell has not been correlated with the ability of any cell to uptake and/or process antigen. As Koski *et al*. do not disclose a rule of nature the skilled artisan standard as of the effective filing date of the invention is used in analyzing Cohen *et al* as a reference for anticipation. Therefore, the skilled artisan at the time of the present invention, viewing the process as taught by Cohen *et al*. would have added antigen to the "activated dendritic-like cells." As above, these "activated dendritic-like cells" are mature dendritic cells that would be unable to process a soluble prostate antigen as previously argued by Applicants.

In view of the remarks above, Applicants respectfully request the Examiner to reconsider and withdraw the rejection of claims 23, 24, and 31-36 under 35 U.S.C. § 102, as obvious over Cohen *et al*. as evidenced by Sallusto *et al*., Koski *et al*., and Czerniecki *et al*.

Rejections Under 35 U.S.C. § 103:

Claim 26 has not been entered and remains rejected under 35 U.S.C. § 103 as obvious over Cohen *et al*. in view of Lutz *et al*. for the reasons of record. In particular, the Examiner believes that the presently claimed dendritic cells are not patentably distinct from the dendritic cells taught by Cohen *et al*.. Lutz *et al*. has been cited by the Examiner as teaching methods for the immortalization of cells. As above, Applicants have again demonstrated that Cohen *et al*. neither explicitly or inherently disclose the dendritic cells of the present invention. Therefore, Lutz *et al*. adds nothing to render obvious the immortalized dendritic cells of the present invention.

Claim 28 and 29 have not been entered and remain rejected under 35 U.S.C. § 103 as being obvious over Cohen *et al*. in view of Taylor *et al*. for the reasons of

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record. In particular, the Examiner believes that the presently claimed dendritic cells are not patentably distinct from the dendritic cells taught by Cohen *et al.* Taylor *et al.* has been cited by the Examiner as teaching cryopreservation techniques. As above, Applicants have again demonstrated that Cohen *et al.* neither explicitly or inherently disclose the dendritic cells of the present invention. Therefore, Taylor *et al.* adds nothing to render obvious the preserved cells of the present invention.

Claim 30 has not been entered and remains rejected under 35 U.S.C. § 103 as being obvious over Cohen *et al.* in view of Taylor *et al.*, further in view of Lutz *et al.* for the reasons of record. In particular, the Examiner believes the presently claimed dendritic cells are not patentably distinct from the dendritic cells taught by Cohen *et al.* and the Examiner has alleged that "the motivation to combine the references is obvious, i.e., to use the immortalized dendritic cells and to be able to maintain the cell for long term in vitro, by immortalizing and preserving the previously isolated cells, as taught by Taylor *et al.* and Lutz *et al.*" As above, Applicants have shown that Cohen *et al.* do not explicitly or inherently disclose or suggest the dendritic cells of the present invention. Therefore, there is no motivation for the skilled artisan to combine the references as suggested by the Examiner.

Claim 37 has also not been entered in the Advisory Action and remains rejected under 35 U.S.C. § 103 as obvious over Cohen *et al.* in view of Stites *et al.* for the reasons set forth above. The Examiner has alleged that as the dendritic cells of the present invention are not patentably distinct from those disclosed by Cohen *et al.* that the motivation to combine the references is obvious, i.e., to match HLA antigen as taught by Stites *et al.* with the dendritic cells as taught by Cohen *et al.* As above, Applicants have demonstrated that Cohen *et al.* do not disclose or suggest either explicitly or inherently the dendritic cells of the present invention. Therefore, there is no motivation to combine the references as suggested by the Examiner.

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As Applicants have demonstrated that the primary reference, Cohen *et al.*, does not either explicitly or inherently disclose or suggest the dendritic cells of the present invention, no motivation is present to combine Cohen *et al.* with any of the secondary references, either individually or in any combination. Therefore, Applicants respectfully request the Examiner the reconsider and withdraw the rejections under 35 U.S.C. § 103 of claims 26, 28 - 30 and 37 as obvious over Cohen *et al.* either alone or in view of any combination of Lutz *et al.*, Taylor *et al.*, or Stites *et al.*.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and an action to that end is urged. If the Examiner believes a telephone conference would aid in the prosecution of this case in any way, please call the undersigned at 206-467-9600.

Respectfully submitted,

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